Non-Technical Summary of Protocol

This study examines the feasibility of using gene therapy to prevent some of the toxicities of an intensive chemotherapy regimen in patients with metastatic breast cancer. Patients who do not wish to participate in the gene therapy procedures will be offered identical chemotherapy on a different protocol. Patients will be treated initially with chemotherapy which is active against breast cancer, but which has a low potential to hurt blood-forming cells (methotrexate, fluorouracil and leucovorin). Then, the patient will receive high dose chemotherapy (cyclophosphamide), during which time blood cells which are capable of rebuilding patients' bone marrows will be removed from the patients' bloodstream. We will use these blood cell collections to isolate peripheral blood progenitor cells (PBPCs), those cells which are thought to be the forbears of all other blood cells.

A portion of the PBPCs will be exposed to a disabled virus which either carries genetic material referred to as the multidrug resistance gene (*MDR1*) . The virus will transfer the *MDR1* gene into a portion of the patient's PBPCs. The purpose of putting the *MDR1* gene into the patients' PBPCs is to try to make these blood cells and their offspring resistant to the toxic effects of certain types of breast cancer chemotherapy. The *MDR1* protein (Pgp) that is made from the *MDR1* gene makes cells resistant to chemotherapy in laboratory systems by pumping the drug out of cells before the drug is able to kill the cell. Another portion of the patients PBPCs will be exposed to a similar disabled virus carrying a different gene called the NeoR gene. The NeoR gene should not change the effects of chemotherapy on blood forming cells. The purpose of using the NeoR gene is that it will serve as a point of comparison, to see if the presence of the *MDR1* drug resistance gene really helps blood forming cells withstand subsequent chemotherapy.

After the next treatment with a high dose of another anti-breast cancer drug which is very toxic to bone marrow cells (thiotepa), patients will be given back their PBPCs, which contain the new genes, to help them recover from the chemotherapy. After recovery, patients will receive four treatments of high-dose paclitaxel (Taxol) and then another four treatments with doxorubicin (Adriamycin). Both of these drugs are very active against breast cancer, and the *MDR1* gene may potentially protect bone marrow cells against these drugs. Samples of peripheral blood cells will be obtained before each of these doses of chemotherapy to determine whether the number of blood cells that contain the *MDR1* gene in comparison to the number that contain the NeoR gene has increased in response to the chemotherapy. The patients' blood counts will also be studied to try to determine whether the *MDR1* gene has provided clinically meaningful protection from chemotherapy.